Relationship Between Attrition and Neurodevelopmental Impairment Rates in Extremely Preterm Infants at 18 to 24 Months

A Systematic Review

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Objective: To assess the effect of loss to follow-up rates at 18 to 24 months on neurodevelopmental outcome statistics for infants of less than 1000 g birth weight or less than 28 weeks' gestational age.

Data Sources: MEDLINE, EMBASE, PubMed, and Cochrane Library databases (January 1, 2000, to June 30, 2010).

Study Selection: We searched for studies reporting outcomes of infants of less than 1000 g birth weight or less than 28 weeks' gestational age who were born after 1990.

Main Exposure: Eligible articles had to report the primary outcome and follow-up rates at 18 to 24 months.

Main Outcome: Our primary composite outcome of neurodevelopmental impairment (NDI) was any of a mental developmental quotient 2 SDs below the mean, using the Bayley Scales of Infant Development II; cerebral palsy; visual impairment; or significant hearing impairment.

Results: Of 43 publications describing outcomes at 18 to 24 months, 20 provided rates of follow-up, describing a total of 34,185 infants. The NDI rates ranged between 12.4% and 57.5%. Follow-up rates ranged between 71.6% and 100%. Higher rates of NDI were significantly correlated with greater loss to follow-up ($r^2=0.38$, $P=.007$). Higher rates of both NDI and loss to follow-up were seen in the United States compared with Canada, the United Kingdom, Finland, Denmark, Austria, Germany, and Australia ($r^2=0.70$, $P=.001$).

Conclusions: Ascertainment bias may overestimate NDI in extremely low-birth-weight or extremely low-gestational-age survivors at 18 to 24 months. Alternatively, the characteristics of different populations and health systems may contribute to higher rates of attrition and higher rates of NDI.


NEURODEVELOPMENTAL outcomes of surviving, extremely, preterm infants are potentially influenced by individual infant and parental factors and by care delivered in the perinatal and neonatal periods. Wide between-site variations exist in rates of survival, neonatal morbidity, and long-term outcomes.1-3 Even after adjusting outcomes for demographics, degree of prematurity, and antenatal interventions, a substantial amount of variation between centers remains unexplained.3 Most attention focuses on quality of care. However, although some loss to follow-up, with its associated ascertainment bias, is inevitable in long-term studies, high rates of loss to follow-up may result in substantial bias and represent another potential source of variation.4-6

Follow-up bias is described in both the adult and pediatric literature.7-10 Bias resulting from incomplete outcome ascertainment can distort the data in opposite directions. Those who do not return for follow-up may be healthier than those who are successfully monitored, making outcomes appear worse than they are.7-10 Alternatively, those who do not attend follow-up may be sicker or more impaired than their peers who are monitored, making outcomes appear better than they are.11-17 We performed a systematic review to assess the extent of between-center variation in recently published 18- to 24-month neurodevelopmental impairment (NDI) rates of extremely low-birth-weight (ELBW) or extremely low-gestational-age (ELGA) infants. We hypothesized that a significant relationship exists between the loss to follow-up rate and the observed rate
of NDI and, further, that the follow-up rates differ between the United States and the rates of other developed countries.

METHODS

PRIMARY OUTCOME

The primary outcome was the rate of NDI in ELBW or ELGA survivors at 18 to 24 months cited in each eligible report. Neurodevelopmental impairment was defined as the presence of at least 1 of the following: a mental developmental quotient 2 SDs below the age and sex standardized mean, using the Bayley Scales of Infant Development II (BSID-II);16 cerebral palsy; visual impairment; or significant hearing impairment. Cerebral palsy was defined as nonprogressive motor impairment characterized by abnormal muscle tone in at least 1 extremity and a decreased range or control of movements. Visual impairment was defined as a visual acuity of less than 20 of 200 unilaterally or bilaterally or classification as blind. Hearing impairment was defined as hearing loss requiring unilateral or bilateral amplification. This composite primary outcome of NDI is clinically relevant as hearing loss requiring unilateral or bilateral amplification. Other diagnoses, such as convulsions.

Eligible studies

For each eligible study, all reported components of NDI and follow-up rates were extracted. We also extracted additional summary baseline data (maternal age, race, educational level, and marital status; infant sex and birth weight; year of birth, country of birth, and outborn/inborn status; Score for Neonatal Acute Physiology or Clinical Risk Index for Babies Severity of Illness scores; and the use of antenatal corticosteroids) to enable risk adjustments for the outcomes of NDI. Two independent searchers (U.G. and S.D.) extracted data. Disagreements were resolved by consensus.

STATISTICAL ANALYSIS

A funnel plot for proportions and percentages was used to investigate the possibility of publication bias. The relationship between NDI rates and follow-up rates in studies reporting all components of NDI was analyzed using a weighted linear regression model. We assumed a random effects model with a binomial within-study variance and an extra between-study variance component. The latter variance component was estimated iteratively from the residual variance after fitting the weighted model. We did not specifically assess model fit, although the residual variance in the final weighted model was close to unity, which supports the validity of the assumed variance structure. The relationship between the individual components of NDI and follow-up rates was also analyzed. The model was adjusted for the baseline variables described in the “Data Extraction” subsection when possible. A secondary sensitivity analysis was performed using the cohorts with slightly different definitions of NDI. All analyses were completed using commercial software (Stata/IC, version 10.0; StataCorp), and P < .05 was considered statistically significant.

RESULTS

Eligible studies

Three searchers (U.G., S.D., and L.M.) obtained good agreement on the inclusion and exclusion of studies (κ = 0.8) and on the extraction of data (κ = 0.85). We found 111 publications reporting outcomes of ELBW or ELGA infants. Forty-three of these publications described outcomes at 18 to 24 months; however, only 20 included rates of follow-up for a total of 24 different cohorts. Eighteen of the 24 cohorts contained data that met our a priori definition of NDI. The remaining 6 cohorts used definitions of NDI that differed slightly from ours (Table 1). These were included in a secondary sensitivity analysis. The funnel plot was symmetrical, indicating a low likelihood of publication bias.

Outcomes

The NDI and follow-up rates were reported for a total of 34,185 ELBW or ELGA infants at 18 to 24 months. Year and country of birth for all 20 publications and 24 cohorts are summarized in Table 1. Follow-up rates ranged from 71.6% to 100% (Table 1). Overall rates of NDI in survivors at 18 to 24 months ranged from 12.4% to 57.5%. There was also a marked variation in the prevalence of the individual components of NDI across all 24 cohorts (Table 2). Cerebral palsy was diagnosed in 5.9% to 33%
of infants. Developmental quotient 2 SDs below average ranged from 16.0% to 54.2%. Rates of hearing impairment ranged from none to 9%. Visual impairment rates ranged from 16.0% to 54.2%. Rates of hearing impairment were also reported for cohorts with greater loss to follow-up, irrespective of the year of birth ($r^2 = 0.38, P = .007$) (Figure 1). For every 1% decrease in the follow-up rate, there was a 0.86% increase in the rate of NDI. In a secondary analysis, we included the 6 remaining cohorts, with slightly different definitions of NDI. Three of these had broader definitions of NDI: they included infants who had died, who had convulsions, or who had received shunts for hydrocephalus. After inclusion of these 6 cohorts, the significant association between follow-up rates and NDI rates remained and was even stronger ($r^2 = 0.43, P < .001$). For every 1% decrease in the follow-up rate, there was a 1.1% increase in the rate of NDI across all infants. When only the data from the 11 cohorts that assigned the lowest possible score to children who were too disabled to be assessed were analyzed, a significant association between follow-up rates and NDI remained ($r^2 = 0.44, P = .03$). Such a subgroup analysis was not possible in the cohorts that excluded these children because of limited numbers.

FOLLOW-UP AND NDI

Using data from the 18 cohorts meeting the a priori definition of NDI, there was a significant association between follow-up rates and rates of NDI. Higher rates of NDI were reported for cohorts with greater loss to follow-up, irrespective of the year of birth ($r^2 = 0.38, P = .007$) (Figure 1). For every 1% decrease in the follow-up rate, there was a 0.86% increase in the rate of NDI. In a secondary analysis, we included the 6 remaining cohorts, with slightly different definitions of NDI. Three of these had broader definitions of NDI: they included infants who had died, who had convulsions, or who had received shunts for hydrocephalus. After inclusion of these 6 cohorts, the significant association between follow-up rates and NDI rates remained and was even stronger ($r^2 = 0.43, P < .001$). For every 1% decrease in the follow-up rate, there was a 1.1% increase in the rate of NDI across all infants. When only the data from the 11 cohorts that assigned the lowest possible score to children who were too disabled to be assessed were analyzed, a significant association between follow-up rates and NDI remained ($r^2 = 0.44, P = .03$). Such a subgroup analysis was not possible in the cohorts that excluded these children because of limited numbers.

FOLLOW-UP AND INDIVIDUAL COMPONENTS OF NDI
each component of NDI was analyzed. We found a significant association between follow-up rates and the reported rates of developmental quotient less than 2 SDs below average. Higher rates of cognitive disability were seen in cohorts with greater loss to follow-up ($r^2=0.24$, $P=.047$). For every 1% decrease in the follow-up rate, there was a 0.55% apparent increase in the rate of cognitive disability. Year of birth was also associated with rates of cerebral palsy. Higher rates of cerebral palsy were seen in older cohorts ($r^2=0.22$, $P=.049$). For every decrease in year, there was a 0.65% increase in the rate of cerebral palsy.

COUNTRY AND NDI

Using the data from all 24 cohorts, we examined the relationships between the rates of NDI and the rates of follow-up by country of origin (Figure 2). We excluded 1 study from the Netherlands because it included death in the composite 18- to 24-month outcome. We used a linear regression model and adjusted for year of birth and country of birth. Country of birth was designated as either United States or non–United States. The model suggests a relationship between country of birth and the rate of

### Table 2. Characteristics of Components of NDI

<table>
<thead>
<tr>
<th>Source</th>
<th>NDI (No./Total No. %)</th>
<th>CP (No./Total No. %)</th>
<th>DQ &lt; -2 SDs (No./Total No. %)</th>
<th>Deaf (No./Total No. %)</th>
<th>Blind (No./Total No. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams-Chapman et al,2008</td>
<td>1790/5740 (31.2)</td>
<td>118/6061 (1.9)</td>
<td>671/6098 (11.0)</td>
<td></td>
<td></td>
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<tr>
<td>Doyle et al,2004</td>
<td>40/219 (18.3)</td>
<td>2/219 (0.9)</td>
<td>5/219 (2.3)</td>
<td></td>
<td></td>
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<tr>
<td>Doyle et al,2010</td>
<td>2/148 (1.4)</td>
<td>4/148 (2.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gargus et al,2009</td>
<td>48/3150 (1.5)</td>
<td>24/3150 (0.8)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hack et al,2000</td>
<td>92/210 (43.8)</td>
<td>20/221 (9.0)</td>
<td>2/22 (9.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hintz et al,2006</td>
<td>34/2536 (1.3)</td>
<td>26/2543 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hintz et al,2005</td>
<td>120/467 (26.6)</td>
<td>5/467 (1.1)</td>
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<tr>
<td>Jacobs et al,2000</td>
<td>10/274 (3.6)</td>
<td>6/274 (2.2)</td>
<td></td>
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<tr>
<td>Kamper,2004</td>
<td>18/195 (23.1)</td>
<td>35/198 (17.9)</td>
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<tr>
<td>Lainwala et al,2007</td>
<td>67/4198 (1.6)</td>
<td>35/4198 (0.8)</td>
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<tr>
<td>Mercier et al,2010</td>
<td>72/3229 (22.3)</td>
<td>62/3240 (1.9)</td>
<td>41/3537 (1.2)</td>
<td></td>
<td></td>
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<tr>
<td>Rijken et al,2003d</td>
<td>2/28 (7.1)</td>
<td>1/28 (3.6)</td>
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<tr>
<td>Salt et al,2006</td>
<td>2/242 (0.8)</td>
<td>7/242 (2.9)</td>
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<td>Sommer et al,2007b</td>
<td>3/48 (6.3)</td>
<td>7/48 (14.6)</td>
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<tr>
<td>Tommska,2003</td>
<td>6/184 (3.3)</td>
<td>3/197 (1.5)</td>
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<tr>
<td>Vohr et al,2004</td>
<td>38/1101 (3.5)</td>
<td>36/1101 (3.3)</td>
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<td>Vohr et al,2005</td>
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<td>38/1101 (3.3)</td>
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<tr>
<td>Wilson-Costello et al,2005</td>
<td>16/1042 (25.7)</td>
<td>30/417 (7.2)</td>
<td>3/417 (0.7)</td>
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<tr>
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<td>1/152 (0.7)</td>
<td>2/152 (1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CP, cerebral palsy; DQ, developmental quotient; NDI, neurodevelopmental impairment.

a Bayley Scales of Infant Development I used for first cohort.

b Individual numbers not provided.

c Evaluated DQ using the Scheffzek scale.

d Used BSID-I.

e Used DQ below –3 SDs, using the Griffiths scale in definition of NDI.

Figure 1. Scatterplot showing the relationship between neurodevelopmental impairment and follow-up rate. Solid line represents the linear regression fit across all subjects.

Figure 2. Scatterplot showing the relationship between neurodevelopmental impairment and follow-up rate by country. Solid line represents the linear regression fit across all subjects.
NDI ($r^2=0.70, P=.001$). Higher rates of NDI were seen when the country of birth was designated as the United States.

**COMMENT**

This systematic review of recent outcome data for ELBW and ELGA infants suggests that higher losses to follow-up are associated with higher rates of NDI at 18 to 24 months. For every 1% decrease in the follow-up rate, there was a 0.86% increase in the rate of NDI. One possible interpretation of our results is that follow-up or ascertainment bias may overestimate NDI in ELBW or ELGA survivors at 18 to 24 months. Parents of children who appear “healthy” and without deficits may believe that there is no need for further evaluation and therefore may not adhere to follow-up.

Studies in the adult and pediatric literature of the relationship between follow-up rates and outcome data offer conflicting conclusions about the direction and magnitude of ascertainment bias. Patients in a treatment program for substance abuse who did not participate in follow-up interviews felt they had “closed that chapter” in their lives and were doing well. Similarly, a 10-year follow-up of men treated for prostate cancer showed that those who attended follow-up had significantly worse outcomes than did men who were lost initially but were assessed after a “vigorous” search. In these 2 studies, loss to follow-up resulted in overestimation of poor outcomes. In contrast, others suggest that loss to follow-up may underestimate poor outcomes. Stinchfield et al found that difficult-to-contact adolescents in a substance abuse treatment program were doing worse at 6 and 12 months compared with their adherent peers. Moreover, in several mental health outcome studies, rates of mental disorders and rates of serious psychosis were underestimated because of dropouts.

Contradictory findings are also present in the neonatal outcome literature. Tin et al conducted an extensive search for infants younger than 32 weeks’ gestation who had been difficult to monitor with routine methods and evaluated all infants who by routine follow-up would have been lost. On testing, those infants had up to 8-fold higher disability rates than their more easily monitored peers. In Australia, Callanan et al found, in a cohort of very low-birth-weight children, that those followed-up with ease at 5 years had better outcomes than those monitored with more difficulty. Hille et al evaluated prematurely born adolescents at 14 and 19 years. Those who were initially lost to follow-up in the first 10 years of life were significantly more likely to have severe disabilities and were more likely to be enrolled in special education compared with adolescents who were easily monitored. In contrast, Castro et al modeled data from the Eunice Kennedy Shriver National Institute of Child Health & Development (NICHD) follow-up records to predict the likelihood of poor outcomes for children with no follow-up and found that, compared with those who were nonadherent to follow-up, children who were adherent appeared to have higher rates of adverse outcomes. McCormick et al followed up children aged 9 to 10 years who had participated in an assessment for developmental status at 1 year and found that more seriously disabled children were easier to locate and evaluate because they required ongoing interaction with health services compared with healthy children. Finally, Mercier et al reported on the neurodevelopmental outcomes of ELBW infants from the Vermont-Oxford Network and the characteristics associated with severe disability and found that follow-up rate was not associated with an increased or decreased risk of severe disability.

Our systematic review suggests that ELBW and ELGA infants who are lost to follow-up may be healthier than infants who are seen at 18- to 24-month follow-up. Our sensitivity analysis included 6 additional cohorts with differing definitions of NDI and did not change this observed association. Our secondary analyses suggest that the apparent rates of one component of NDI, developmental quotient less than 2 SDs below average, rise as loss to follow-up increases. The secondary analysis also suggests that rates of cerebral palsy are associated with year of birth. Infants born in more recent years have lower rates of cerebral palsy, perhaps reflecting changes in clinical practice.

Variations in the follow-up rate by the country of birth may have implications for the interpretation of studies (Figure 2). The neonatal literature has frequently examined variation of neonatal intensive care unit outcomes within countries; however, between-country differences also exist. The significant relationship that we observed between follow-up rates of NDI may be confounded by country of birth. It is possible that the generally lower follow-up rates in the United States may be a cause of spuriously high NDI rates in US cohorts compared with cohorts from other developed countries, as represented in this review. Alternatively, the characteristics of different populations, as well as cultural and health system factors, may contribute to both higher rates of attrition and higher rates of NDI in the United States. In an evaluation of participant loss in longitudinal follow-up of patients enrolled in a multicenter clinical trial, Aylward et al found that urban African Americans and Latinos were much more likely to drop out than were suburban or rural white families. Participants with lower socioeconomic status and decreased social support were prone to loss to follow-up. Constantine et al and Wolke et al found that low maternal educational level was associated with increased dropout rates regardless of infant outcome. Unfortunately, we could not directly examine potentially confounding patient characteristics because such data were not available in all eligible publications; therefore, our results should be treated with caution. Furthermore, because of the small number of publications identified for this review, analysis with a large number of variables would not have been possible.

One major limitation of this study is that there is some overlap in the infants in some of the published studies from the United States. For example, Adams-Chapman et al reviewed infants from the 19 centers in the NICHD Neonatal Network follow-up program born in 1993 through 2002, and Vohr et al reviewed children born in 1993 and 1994 in 12 centers in the same network. Wilson-Costello et al reported on infants born in 1990 through 1998 in a single center that is a site of the NICHD.
Neonatal Network. It is possible that some of the infants considered for one publication were also part of another publication. We were unable to account for which or how many infants were included in multiple publications. We also did not seek data from unpublished studies. The authors of eligible articles adopted an inconsistent approach with regard to the inclusion of infants who were severely handicapped and could not be formally tested with the BSID-II. Some studies included these infants and assigned them the lowest possible score, whereas other authors excluded them from analysis. Excluding children with severe disabilities who are untestable with the BSID-II would falsely lower the reported rates of NDI. It was not always possible to quantify how many of these children were excluded and whether this alone was a significant source of the variation in NDI rates. However, a significant association between follow-up and NDI was seen when only the cohorts that assigned the lowest possible score were analyzed.

Of 39 reports on 18- to 24-month outcomes, only 20 reported rates of follow-up. This further highlights the need for more transparency in the reporting of attrition rates.

In conclusion, ascertainment bias may overestimate NDI in ELBW or ELGA infants at 18 to 24 months. Alternatively, the characteristics of different populations and health systems may contribute to both higher rates of attrition and higher rates of NDI.

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Author Contributions: Dr Kirpalani had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Guillén, Schmidt, and Kirpalani. Acquisition of data: Guillén, DeMauro, and Ma. Analysis and interpretation of data: Guillén, DeMauro, Zupancic, Roberts, Schmidt, and Kirpalani. Drafting of the manuscript: Guillén and Schmidt. Critical revision of the manuscript for important intellectual content: Guillén, DeMauro, Ma, Zupancic, Roberts, Schmidt, and Kirpalani. Statistical analysis: Ma, Zupancic, and Roberts. Administrative, technical, and material support: Kirpalani. Supervision: Schmidt and Kirpalani. Financial Disclosure: None reported.

REFERENCES


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